

**EUROPEAN PATENT APPLICATION**

(12)

(21) Application number: 86300808.2

(22) Date of filing: 06.02.86

(51) Int. Cl.: C 07 D 401/12, C 07 D 401/14,  
C 07 D 409/14, A 61 K 31/47



(30) Priority: 11.02.85 GB 8503416  
12.07.85 GB 8517675

(43) Date of publication of application: 20.08.86  
Bulletin 86/34

(84) Designated Contracting States: AT BE CH DE FR GB IT  
LI LU NL SE

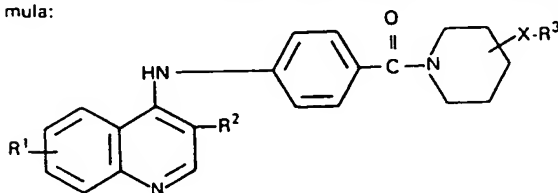
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(54) Piperidine compound.

(57) This invention provides a piperidine compound of the for-  
mula:



wherein

R<sup>1</sup> is hydrogen or trihalomethyl,

R<sup>2</sup> is hydrogen or protected carboxy,

R<sup>3</sup> is heterocyclic group or aryl which may have halogen, and

X is -S-, -S-, S-, -O-, -NH- or lower alkylene which may have  
hydroxy.

and pharmaceutically acceptable salt thereof.

This compound possesses hypotensive activity and are  
useful as anti-hypertensive agent. The invention further relates  
to processes for the preparation of this compound and phar-  
maceutical composition comprising compound of the above  
formula.

EP 0 191 603 A2

PIPERIDINE COMPOUND

This invention relates to a new piperidine compound. More particularly, it relates to a new piperidine compound and pharmaceutically acceptable salt thereof which have an antihypertensive activity, to a process for the preparation thereof, and to a pharmaceutical composition comprising the same.

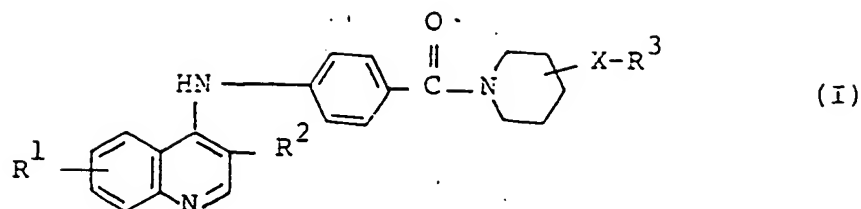
Accordingly, it is an object of this invention to provide a new piperidine compound and pharmaceutically acceptable salt thereof which are useful as an antihypertensive agent.

Another object of this invention is to provide a process for the preparation of the piperidine compound.

Further object of this invention is to provide a pharmaceutical composition comprising the piperidine compound as an active ingredient.

The piperidine compound of this invention can be represented by the following formula :

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wherein  $R^1$  is hydrogen or trihalomethyl,  
 $R^2$  is hydrogen or protected carboxy,  
 $R^3$  is heterocyclic group or aryl which may have  
 halogen, and

10

$$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{X is } -\text{S}-, -\text{S}-, -\text{S}-, -\text{O}-, -\text{NH}- \text{ or lower alkylene} \\ \parallel \\ \text{O} \end{array}$$

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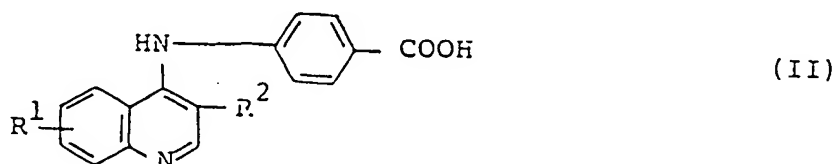
which may have hydroxy,  
 and pharmaceutically acceptable salt thereof.

Suitable pharmaceutically acceptable salts of the  
 piperidine compound (I) are inorganic or organic acid  
 addition salts such as hydrochloride, hydrobromide,  
 20 sulfate, nitrate, acetate, p-toluenesulfonate and the  
 like.

According to this invention, the new piperidine  
 compound (I) and pharmaceutically acceptable salt thereof  
 can be prepared by, for example, the following processes.

25

Process 1 :

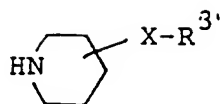


or its reactive derivative  
 at the carboxy group  
 or salt thereof

35

+

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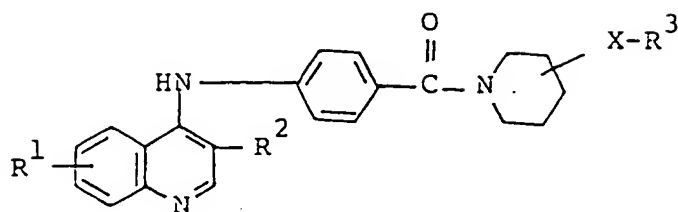
(III)

or its reactive derivative  
at the amino group  
or salt thereof

5



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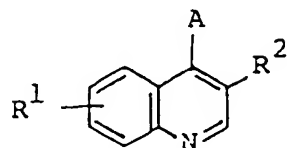
(I)

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or salt thereof

Process 2 :

20

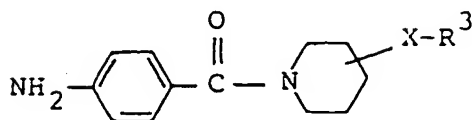


(IV)

25

or salt thereof

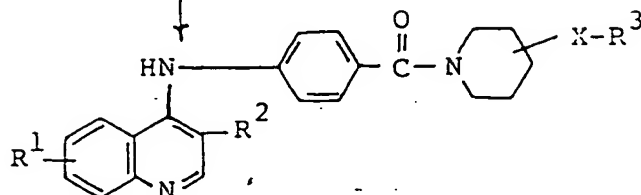
+



(V)

30

or salt thereof



(I)

35

or salt thereof

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wherein  $R^1$ ,  $R^2$ ,  $R^3$  and X are each as defined above and A is acid residue.

5 In the above and subsequent descriptions of this specification, suitable examples and illustrations of the various definitions are explained in detail in the followings.

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

10 "Trihalomethyl" may include trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl and the like.

15 "Protected carboxy" may include esterified carboxy such as lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl) and the like.

20 "Heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and preferred "heterocyclic group" may be 5 or 6-membered heteromonocyclic group containing nitrogen or sulfur atom such as pyridyl, thienyl and the like.

25 "Aryl" may include phenyl, tolyl, naphthyl and the like.

"Halogen" may include fluorine, chlorine, bromine, iodine and the like.

30 "Lower alkylene" may include methylene, ethylene, trimethylene and the like.

"Acid residue" may include halogen (e.g. chlorine, bromine, iodine, fluorine, etc.) and the like.

35 Suitable salts of the starting compound (II) or its reactive derivative at the carboxy group may include an acid addition salt mentioned above and a salt

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with a base such as sodium salt, potassium salt, triethylamine salt and the like.

Suitable salts of the starting compound (III), (IV) and (V) may include inorganic or organic acid addition salt mentioned above.

Preferable embodiments of the object compound (I) are as follows.

Preferable embodiments of  $R^1$  is trihalomethyl (more preferably trifluoromethyl);  $R^2$  is hydrogen or protected carboxy [more preferably esterified carboxy (most preferably lower alkoxy carbonyl)];  $R^3$  is 5 or 6-membered heteromonocyclic group containing nitrogen or sulfur atom (more preferably pyridyl or thienyl) or aryl which may have halogen (more preferably phenyl which may have halogen);

X is -S-,  $\begin{array}{c} \text{O} \\ \parallel \\ \text{-S-} \end{array}$ ,  $\begin{array}{c} \text{O} \\ \parallel \\ \text{-S-} \\ \parallel \\ \text{O} \end{array}$ , -O-, -NH- or lower alkylene which may have hydroxy.

The processes as illustrated above are explained in more detail in the followings.

#### Process 1 :

The object compound (I) or salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the carboxy group or salt thereof with the compound (III) or its reactive derivative at the amino group or salt thereof.

The starting compound (II) includes novel and known ones. For example, 4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoic acid and preparation thereof are disclosed in Japan Kokai No. 18479/75 and novel compounds among the starting compound (II) can be prepared in a similar manner thereto.

The starting compound (III) includes novel and

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known ones. For example, 4-[(4-fluorophenyl)amino]-  
piperidine and preparation thereof are disclosed in  
U.S. Patent No. 3691176 (1982) and some of novel  
compounds among the starting compound (III) can be  
5 prepared in a manner described in Examples as mentioned  
below. The other compounds can be prepared in a similar  
manner thereto.

The reactive derivative at the carboxy of the  
compound (II) may include acid halide (e.g. acid  
10 chloride, acid bromide, etc.), acid anhydride, acid  
azide, activated amide or activated ester (e.g.  
succinimide ester, etc.), and the like.

The reactive derivative at the amino group of  
15 the compound (III) may include a silyl derivative  
formed by the reaction of the compound (III) with a  
silyl compound (e.g. bis(trimethylsilyl)acetamide,  
trimethylsilylacetamide, etc.) and the like.

20 The reaction can preferably be conducted in the  
presence of an organic or inorganic base such as alkali  
or alkaline earth metal hydroxide (e.g. sodium hydroxide,  
potassium hydroxide, calcium hydroxide, etc.), alkali  
or alkaline earth metal carbonate or bicarbonate (e.g.  
25 sodium carbonate, potassium carbonate, sodium bicarbonate)  
alkali or alkaline earth metal alkoxide (e.g. sodium  
ethoxide, lithium methoxide, magnesium methoxide),  
trialkylamine (e.g. triethylamine), pyridine, bicyclodiaz  
compound (e.g. 1,5-diazabicyclo[3,4,0]nonene-5,1,5-  
30 diazabicyclo[5,4,0]undecene-5, etc.) and the like.

When the starting compound (II) is used in a form  
of free acid, the reaction of this process may preferably  
be conducted in the presence of a condensing agent such  
as carbodiimidic compound (e.g. N,N'-dicyclohexylcarbodi-  
35 imide, N-cyclohexyl-N'-morpholinoethylcarbodiimide,

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N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.), N,N'-carbonyldiimidazole, N,N'-carbonyldi(2-methyl-  
5 imidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, alkoxyacetylene, 1-alkoxy-1-chloroethylene, trialkylphosphite, ethyl polyphosphate, isopropyl polyphosphate, phosphorus compound (e.g. phosphorus oxychloride, phosphorus  
10 trichloride, etc.), thionyl chloride, oxalyl chloride, 2-ethyl-7-hydroxybenzisoaxazolium salt, 2,2,4,4,6,6-hexachloro-1,3,5,2,4,6-triazatriphosphorine, 1-benzenesulphonyloxy-6-chloro-1H-benzotriazole, p-toluenesulfonyl chloride, isopropoxybenzenesulfonyl  
15 chloride, or a mixed condensing agent such as triphenylphosphine and a carbon tetrahalide (e.g. carbon tetrachloride, carbon tetrabromide, etc.) or so-called Vilsmeier reagent (e.g. a complex of N,N-dimethylformamide with phosphoryl chloride, phosgene  
20 or thionyl chloride, etc.), and the like.

The reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, acetone, dioxane, acetonitrile, ethyl acetate, N,N-dimethylformamide, dimethylsulfoxide,  
25 tetrahydrofuran, methylene chloride, chloroform, pyridine, N-methylmorpholine, N-methylpyrrolidine, etc. or a mixture thereof.

The reaction temperature is not critical and this reaction can be conducted within the temperature range  
30 of cooling to heating.

#### Process 2 :

The compound (I) or salt thereof can be prepared by reacting the compound (IV) or salt thereof with the  
35 compound (V) or salt thereof.

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The compound (V) includes novel and known ones. The detailed method for preparing a novel compound, 1-(4-aminobenzoyl)-4-[(4-fluorophenyl)hydroxymethyl]-piperidine is disclosed in Example 8 (1)-(3) as mentioned below and novel compounds among the starting compound (V) can be prepared in a similar manner thereto or in a conventional manner.

The reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, acetone, dioxane, acetonitrile, ethyl acetate, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dichloromethane, chloroform, pyridine, N-methylmorpholine, N-methylpyrrolidine, etc. or a mixture thereof.

The reaction temperature is not critical and this reaction can be conducted within the temperature range of cooling to heating.

The object compound (I) thus obtained can be purified, isolated from the reaction mixture and converted to the desired salts in a conventional manner.

The piperidine compound(I) has an excellent antihypertensive activity and less side effects(e.g. diarrhea, decreasing of sperm motility, gastric lesion, etc.) and therefore useful as an antihypertensive agent.

The following Tests are given for the purpose of illustrating antihypertensive activity of the object compound (I).

#### Test

##### (a) Test method :

Five-week old male Wister rats were uninephrectomized under anesthesia. Deoxycorticosterone acetate (DOCA) (30 mg/kg), suspended in peanut oil, was injected subcutaneously twice a week and 1% saline was substituted

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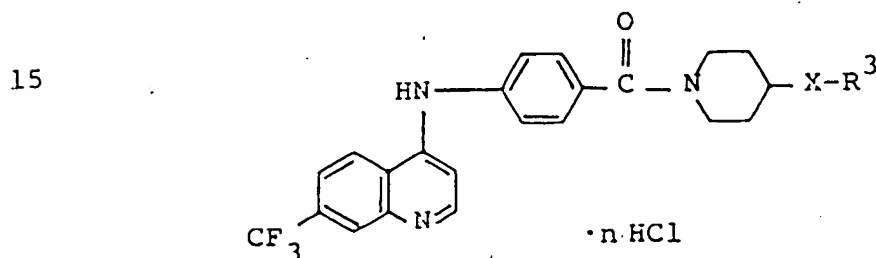
for the drinking water. Animals with mean blood pressure 150-200 mmHg were used for experiment between 5 and 7 weeks after surgery.

5 The test compounds (Dosage : 10 mg/kg) were administered orally to the test animals.

Blood pressure was measured at the femoral artery by means of a pressure transducer and recorded as electrically integrated values of mean arterial pressure.

10 (b) Test compound :

A formula of the compound :



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Test compound No.	X	R <sup>3</sup>	n
25 1	-S-		0
30 2			0
35 3			1

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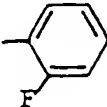
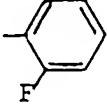
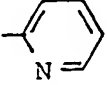
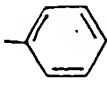
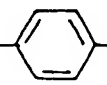
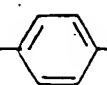
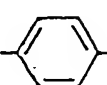
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4	-S-		0
5	$\begin{array}{c} \text{O} \\    \\ -\text{S}- \\    \\ \text{O} \end{array}$		1
6	-S-		2
7	-CH <sub>2</sub> -		1
8	$\begin{array}{c} \text{OH} \\   \\ -\text{CH}- \end{array}$		1
9	-O-		1
10	-NH-		2

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(c) Test result :

The results are shown in the following Table.

5	Test compound No.	Maximum decrease of blood pressure (%)
	1	37
	2	35
	3	44
10	4	34
	5	37
	6	51
	7	32
15	8	44
	9	44
	10	50

20

The piperidine compound (I) can be used as an antihypertensive agent either in free form or in the form of the pharmaceutically acceptable salts such as an acid addition salt (e.g. hydrochloride, sulfate, acetate, p-toluenesulfonate).

25

The object compound (I) or its pharmaceutically acceptable salt can usually be administered to mammals including human beings in the form of a conventional pharmaceutical composition such as capsule, microcapsule, tablet, granule, powder, troche, syrup, aerosol, micronized powder, inhalation, solution, injection, suspension, emulsion, suppository, ointment, or the like.

30

The pharmaceutical composition of this invention can contain various organic or inorganic carrier

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materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g. sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.),  
5 binding agent (cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g. starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch, sodium glycole-starch, sodium bicarbonate,  
10 calcium phosphate, calcium citrate, etc.), lubricant (e.g. magnesium stearate, aerosil, talc, sodium laurylsulfate, etc.), flavoring agent (e.g. citric acid, mentol, glycine, orange powders, etc.),  
15 preservative (sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g. methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous  
20 diluting agent (e.g. water), base wax (e.g. cacao butter, polyethyleneglycol, white petrolatum, etc.).

A dosage of the present active ingredient is to be varied depending on various factors such as weight  
25 and/or age of a patient and/or a stage of the allergic disease, and further the kind of administration route. In general, the optimum dosage of the object compound (I) or its pharmaceutically acceptable salt to human body can be selected within a range of 0.1-100 mg/kg.  
30

The following Examples are given for the purpose of illustrating this invention.

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Example 1

(1) A mixture of 4-chloro-1-methylpiperidine (110.1 g), 2-fluorothiophenol (117.3 g), and potassium carbonate (170.8 g) in N,N-dimethylformamide (1.0 l) was stirred at 90°C for 2 hours and filtered. The filtrate was concentrated in vacuo to give an oily residue, which was diluted with brine and extracted three times with diethyl ether. The extracts were dried over magnesium sulfate, concentrated in vacuo, and distilled to give 4-[(2-fluorophenyl)thio]-1-methylpiperidine (111.1 g) as a yellow oil.

bp : 119-123°C/0.4 mmHg

IR (film) : 3060, 2930, 2840, 2780, 2720,  
2670  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.3-2.2 (6H, m), 2.25 (3H, s),  
2.65-3.35 (3H, m), 6.85-7.65 (4H, m)

(2) A solution of phenyl chlorocarbonate (91.4 g) in dry methylene chloride (269 ml) was added dropwise to a stirred solution of 4-[(2-fluorophenyl)thio]-1-methylpiperidine (107.6 g) in dry methylene chloride (538 ml) under ice-cooling over a period of 1.5 hours. The resultant solution was stirred under ice-cooling for 30 minutes and at room temperature for 1.5 hours, then diluted with 1N hydrochloride acid. The methylene chloride layer was separated, washed with 5% sodium hydroxide solution and brine, dried over magnesium sulfate, and chromatographed on silica gel using methylene chloride as an eluent to give a yellow oil (133.9 g). The oil (0.49 g) was crystallized from n-hexane to give phenyl 4-[(2-fluorophenyl)thio]-1-piperidine carboxylate (0.25 g) as colourless powder.

mp : 58-60°C

IR (Nujol) : 1730, 1710  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.3-2.25 (4H, m), 2.85-3.75 (3H, m),  
3.9-4.35 (2H, m), 6.9-7.65 (9H, m)

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(3) 3-Chloroperbenzoic acid (73.2 g) was slowly added to a stirred solution of phenyl 4-[(2-fluorophenyl)-thio]-1-piperidine-carboxylate (122.2 g) in chloroform (1.10 l) under ice-cooling over a period of 25 minutes and the mixture was stirred at the same temperature for 1 hour. Additional 3-chloroperbenzoic acid (66.9 g) was slowly added with stirring at the same temperature over a period of 15 minutes. The resultant mixture was stirred at room temperature for 1 hour and then filtered. The filtrate was washed successively with sodium bisulfite solution, sodium bicarbonate solution, and brine, dried over magnesium sulfate and concentrated to dryness in vacuo. The solid residue was recrystallized from a mixture of diisopropyl ether and ethyl acetate to give phenyl 4-[(2-fluorophenyl)sulfonyl]-1-piperidine-carboxylate (102.2 g) as colourless powder.

mp : 160-161°C

IR (Nujol) : 1740, 1720, 1330, 1150  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.7-2.3 (4H, m), 2.75-3.75 (3H, m), 4.25-4.5 (2H, m), 7.0-8.15 (9H, m)

(4) A mixture of phenyl 4-[(2-fluorophenyl)sulfonyl]-1-piperidine-carboxylate (97.0 g) and 47% hydrobromic acid (1.11 l) was stirred under reflux for 1 hour and concentrated in vacuo. The residue was suspended in water (700 ml). The suspension was adjusted to alkaline pH with 20% sodium hydroxide solution (370 ml) and then extracted twice with methylene chloride. The extracts were combined and dried over magnesium sulfate. After removal of magnesium sulfate, the solution was treated with methanolic hydrochloric acid and concentrated to dryness in vacuo. The powdery residue was washed with ethanol and diethyl ether to give 4-[(2-fluorophenyl)sulfonyl]piperidine hydrochloride (67.85 g) as colorless powder.

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mp : 264-265°C

IR (Nujol) : 2800-2300, 1340, 1320, 1150 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.65-2.35 (4H, m), 2.65-4.0  
(5H, m), 7.35-8.1 (4H, m), 9.4 (2H, broad s)

5

(5) 4-[[7-(Trifluoromethyl)-4-quinolyl]amino]-benzoyl chloride hydrochloride (65.20 g) was added slowly to a stirred mixture of 4-[(2-fluorophenyl)-sulfonyl]piperidine hydrochloride (47.0 g) and  
10 triethylamine (117.2 ml) in dry methylene chloride (1.01 l) at room temperature. The resultant mixture was stirred at the same temperature for 1 hour and under ice cooling for 0.5 hours. The precipitated powder was collected by filtration, washed with a mixture of  
15 methylene chloride and water, and suspended in a mixture of chloroform and methanol. Excess methanolic hydrochloric acid was added to the suspension and the resulting solution was concentrated in vacuo to give an oil. The oil was triturated in a mixture of ethyl acetate and  
20 ethanol to give powdery 4-[(2-fluorophenyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride (46.73 g).

1) The object compound recrystallized from ethanol

IR (Nujol) : 3220-3040 (m), 2500 (broad), 1610,  
25 1590, 1320, 1150 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.45-2.2 (4H, m), 2.8-4.6  
(5H, m), 7.07 (1H, d, J=7Hz), 7.4-8.25  
(9H, m), 8.63 (1H, broad s), 8.67 (1H, d,  
J=7Hz), 9.30 (1H, broad d, J=9Hz),  
30 11.6 (1H, broad)

30

X ray diffraction (Target, Cu; Filter, Ni;  
Voltage, 30 KV; Current, 10 m A; Time constant,  
0.5 second; Scanning speed, 2°/minute; Chart speed,  
35 2 cm/minute; Divergence slit, 1°; Receiving slit, 0.15 m m;  
Scatter slit, 1°) :

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peak No.	1	2	3	4	5
2 $\theta$ (Bragg diffraction angle)	8.3°	13.9°	15.6°	16.6°	17.4°
I/I <sub>0</sub> (relative intensity)	38	23	35	100	29

5

6	7	8	9	10	11	12	13	14	15
18.5°	18.9°	19.3°	20.1°	21.0°	21.4°	22.2°	23.0°	25.0°	25.6°
43	38	33	37	41	48	61	21	35	28

10

16	17	18	19	20	21
26.4°	26.7°	27.1°	27.7°	28.8°	29.6°
41	42	44	27	17	24

Thermal analysis [Atmosphere, N<sub>2</sub> (30 ml/minute);  
Sensitivity, DTA :  $\pm 250\mu$  V, TG :  $\pm 5$  mg;  
Heating rate, 10°C/minute] :  
Melt (225°C)  $\rightarrow$  decomposition (306°C)

15

2) The object compound recrystallized from a mixture of water and ethanol

NMR values are the same as those of the above 1).

20

IR (Nujol) : 3500-3040 (m), 2800-2300 (m), 1640, 1620 (shoulder), 1595, 1560, 1325, 1135 cm<sup>-1</sup>

X ray diffraction [Analysis condition is the same as that of the above 1)] :

25

peak No.	1	2	3	4	5
2 $\theta$ (Bragg diffraction angle)	9.6°	11.6°	12.1°	12.8°	13.6°
I/I <sub>0</sub> (relative intensity)	40	42	31	36	47

30

6	7	8	9	10	11	12	13	14	15
15.6°	17.1°	18.6°	19.3°	19.7°	20.4°	20.9°	21.4°	22.2°	22.9°
37	93	23	100	72	45	44	24	70	58

35

16	17	18	19	20
24.4°	25.6°	27.4°	28.2°	29.0°
48	92	21	38	33

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Thermal analysis [Analysis condition is the same as  
that of the above 1)] :

Dehydration (69°C) → melt (201°C) → decomposition (304°C)

- 5 3) The object compound recrystallized from a mixture  
of methanol and ethyl acetate

NMR values are the same as those of the above 1).

10 IR (Nujol) : 3600-3050 (m), 2800-2350 (m), 1640,  
1620, 1595, 1560, 1325, 1135  $\text{cm}^{-1}$

X ray diffraction [Analysis condition is the same  
as that of the above 1)] :

peak No.	1	2	3	4	5
15 2θ (Bragg diffraction angle)	9.3°	11.7°	13.6°	15.9°	16.9°
I/I <sub>0</sub> (relation intensity)	36	27	27	53	23

6	7	8	9	10	11	12	13	14	15
18.8°	20.9°	21.8°	22.3°	22.9°	23.4°	24.2°	25.3°	27.9°	29.2°
20 100	26	42	38	30	39	28	55	21	23

Thermal analysis [Analysis condition is the same as  
that of the above 1)] :

Melt (197°C) → decomposition (308°C)

- 25 4) The object compound recrystallized from a  
mixture of ethanol and dioxane

NMR values are the same as those of the above 1).

30 IR (Nujol) : 3250-3010 (m), 2800-2200 (m),  
1655 (shoulder), 1615, 1595, 1320, 1165,  
1145, 1130  $\text{cm}^{-1}$

35 X ray diffraction [Analysis condition is the same  
as that of the above 1)] :

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peak No.		1	2	3	4	5
2θ (Bragg diffraction angle)		8.6°	10.5°	11.8°	12.8°	14.5°
I/I <sub>0</sub> (relative intensity)		12	47	27	18	44

5	6	7	8	9	10	11	12	13	14	15
	14.8°	15.8°	16.5°	17.8°	18.4°	18.9°	19.3°	20.2°	20.7°	21.2°
	44	15	28	22	45	25	19	100	24	47

10	16	17	18	19	20	21	22	23	24	25
	21.6°	22.0°	22.2°	22.9°	23.3°	23.7°	24.0°	24.3°	25.2°	25.7°
	21	34	20	42	31	28	22	15	22	24

	26	27	28	29
	26.7°	27.2°	28.3°	29.6°
15	21	16	15	15

Thermal analysis [Analysis condition is the same  
as that of the above 1)] :

Endothermic change (193°C) → exothermic change

### Example 2

(1) The following compound was prepared in a  
similar manner to that of Example 1 (2).

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Phenyl 4-[(4-fluorophenyl)thio]-1-piperidine-carboxylate.

mp : 64-66°C

IR (Nujol) : 1720  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.25-2.25 (4H, m), 2.9-3.45 (3H, m), 3.95-4.4 (2H, m), 6.85-7.6 (9H, m)

(2) The following compound was prepared in a similar manner to that of Example 1 (4).

10 4-[(4-Fluorophenyl)thio]piperidine hydrochloride.

mp : 170-173°C (recrystallized from a mixture of ethyl acetate and isopropanol)

IR (Nujol) : 2800, 2720, 2670, 2560, 2460  $\text{cm}^{-1}$

15 NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.4-2.3 (4H, m), 2.7-3.7 (5H, m), 7.05-7.7 (4H, m), 9.4 (2H, broad s)

(3) 4-[[7-(Trifluoromethyl)-4-quinolyl]amino]benzoyl chloride hydrochloride (0.94 g) was added slowly to a stirred mixture of 4-[(4-fluorophenyl)thio]piperidine hydrochloride (0.60 g) and triethylamine (1.69 ml) in dry methylene chloride (12.5 ml) at room temperature. The resultant mixture was stirred at the same temperature for 3.5 hours. The precipitated powder was collected by filtration and washed with methylene chloride and diethyl ether to give 4-[(4-fluorophenyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]-piperidine (0.45 g) as colourless powder.

mp : 211-214°C

IR (Nujol) : 3300, 1610  $\text{cm}^{-1}$

30 NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.05-2.15 (4H, m), 2.85-4.3 (5H, m), 7.0-8.75 (13H, m), 9.35 (1H, broad s)

Example 3

35 (1) 3-Chloroperbenzoic acid (0.96 g) was slowly added to a stirred solution of 4-[(4-fluorophenyl)thio]-1-

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piperidine hydrochloride (1.2 g) in chloroform (60 ml) under ice-cooling over a period of 5 minutes and the mixture was stirred at the same temperature for 45 minutes. After being treated with sodium bisulfite solution under ice-cooling, the resultant mixture was adjusted to alkaline pH with 20% sodium hydroxide solution. The chloroform layer was separated and the aqueous layer was extracted three times with chloroform. The chloroform layers were combined and dried over magnesium sulfate. After removal of magnesium sulfate, the solution was treated with ethereal hydrochloric acid and concentrated to dryness in vacuo. The powdery residue was washed with isopropanol to give 4-[(4-fluorophenyl)sulfinyl]piperidine hydrochloride (1.10 g) as colourless powder.

mp : 208-210°C

IR (Nujol) : 2730, 2680, 2580, 2460, 1040  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.5-2.1 (4H, m), 2.7-3.5

(5H, m), 7.4-8.05 (4H, m), 9.5 (2H, broad)

(2) 4-[[7-(Trifluoromethyl)-4-quinolyl]amino]-benzoyl chloride hydrochloride (14.7 g) was added slowly to a stirred mixture of 4-[(4-fluorophenyl)sulfinyl]piperidine hydrochloride (10.0 g) and triethylamine (26.4 ml) in dry methylene chloride (440 ml) at room temperature. The resultant mixture was stirred at the same temperature for 3 hours, and concentrated to dryness in vacuo. Water was added to the residue and the precipitated powder was collected by filtration, washed with water, and dried to give a powder. The powder was washed with methylene chloride to give 4-[(4-fluorophenyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine (13.60 g) as colourless powder.

mp : 215-216.5°C

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IR (Nujol) : 3320, 1615, 1565, 1040  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ - $\text{CD}_3\text{OD}$ ,  $\delta$ ) : 1.5-2.15 (4H, m),  
2.65-3.15 (3H, m), 4.15-4.5 (2H, m), 7.1-8.65  
(13H, m)

5

Example 4

(1) A solution of phenyl chlorocarbonate (17.3 g) in dry methylene chloride (40 ml) was dropwise added to a stirred solution of 4-chloro-1-methylpiperidine (13.3 g) in dry methylene chloride (60 ml) under ice-cooling over a period of 5 minutes. The resultant mixture was stirred at the same temperature for 30 minutes and then at room temperature for 6 hours. The mixture was washed with water, dried over magnesium sulfate, and concentrated in vacuo to give an oil, which was distilled to give phenyl 4-chloro-1-piperidine-carboxylate (17.0 g) as a colourless oil.

15

bp : 144-148°C/0.5mmHg

IR (film) : 1730  $\text{cm}^{-1}$

20

NMR ( $\text{CCl}_4$ ,  $\delta$ ) : 1.5-2.3 (4H, m), 3.2-4.3 (5H, m),  
7.0-7.6 (5H, m)

(2) 60% Sodium hydride dispersion in a mineral oil (2.40 g) was slowly added to an ice-cooled solution of phenyl 4-chloro-1-piperidine-carboxylate (15.2 g) and 4-mercaptopyridine (6.66 g) in dry N,N-dimethylformamide (150 ml) with stirring under nitrogen gas. The mixture was stirred at the same temperature for 30 minutes and then at 80°C for 4.5 hours. The resultant reaction mixture was poured into ice-water and extracted with diethyl ether. The extract was washed with water, dried over magnesium sulfate, and concentrated to dryness in vacuo. The crystalline residue was recrystallized from a mixture of n-hexane and isopropanol to give phenyl 4-[(4-pyridyl)-

25

30

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thio]-1-piperidine-carboxylate (15.4 g) as colourless crystals.

mp : 102-104°C

IR (Nujol) : 1725  $\text{cm}^{-1}$

5 NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.7-2.4 (4H, m), 3.0-3.8 (3H, m),  
4.0-4.3 (2H, m), 7.0-8.5 (9H, m)

(3) A solution of phenyl 4-[(4-pyridyl)thio]-1-piperidine-carboxylate (5.0 g) in conc. hydrochloric acid (50 ml) was refluxed for 7 hours and concentrated to dryness in vacuo. The crystalline residue was washed with isopropanol and recrystallized from methanol to give 4-[(4-pyridyl)thio]piperidine dihydrochloride (2.85 g).

15 mp : 275-282°C

IR (Nujol) : 2850-1800  $\text{cm}^{-1}$

NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ) : 1.8-2.7 (4H, m), 3.0-3.8 (4H, m),  
4.13 (1H, m), 7.90 (2H, dd,  $J=7\text{Hz}$ ),  
8.50 (2H, dd,  $J=7\text{Hz}$ )

20

(4) 4-[[7-(Trifluoromethyl)-4-quinolyl]amino]-benzoyl chloride hydrochloride (1.88 g) was added slowly to a stirred mixture of 4-[(4-pyridyl)thio]-piperidine dihydrochloride (1.30 g) and triethylamine (2.92 g) in dry methylene chloride (60 ml) at room temperature. The resultant mixture was stirred at the same temperature for 6 hours and concentrated to dryness in vacuo to give a solid, which was triturated in water and filtered to give light yellow crystals (2.56 g).  
30 The crystals (2.0 g) was dissolved in a mixture of chloroform and ethanol and excess ethanolic hydrochloric acid was added to the solution. The resultant solution was concentrated to dryness in vacuo to give crystals, which were washed with isopropanol and recrystallized  
35 from ethanol to give 4-[(4-pyridyl)thio]-1-[4-[[7-

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(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine dihydrochloride (1.26 g) as pale yellow crystals.

mp : 221-225°C

IR (Nujol) : 2560, 1620, 1590  $\text{cm}^{-1}$

5 NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.6-2.2 (4H, m), 3.0-4.3 (5H, m), 7.0-9.4 (13H, m)

#### Example 5

10 (1) 30% Hydrogen peroxide (10 ml) was added dropwise to a stirred solution of 4-[(4-pyridyl)thio]-piperidine dihydrochloride (2.0 g) in acetic acid (30 ml) at room temperature over a period of 20 minutes and the mixture was stirred at the same temperature for 40 minutes. Then the mixture was stirred at 70°C for 15 8 hours and additional 30% Hydrogen peroxide (10 ml) was added. The resultant mixture was stirred at 70°C for 1 hour, treated with excess sodium sulfite under ice-cooling, and concentrated in vacuo. The residue was dissolved in water. The solution was adjusted to 20 alkaline pH with 5N aqueous potassium hydroxide and extracted several times with chloroform. The extracts were collected, dried over magnesium sulfate, and concentrated to dryness in vacuo. The crystalline residue was recrystallized from isopropanol to give 25 4-[(4-pyridyl)sulfonyl]piperidine (0.87 g).

mp : 88-91°C

IR (Nujol) : 3300, 3200, 1320, 1150  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.5-3.5 (10H, m), 7.8-9.0 (4H, m)

30 (2) 4-[[7-(Trifluoromethyl)-4-quinolyl]amino]-benzoyl chloride hydrochloride (0.90 g) was added slowly to a stirred mixture of 4-[(4-pyridyl)sulfonyl]piperidine (0.50 g) and triethylamine (0.70 g) in dry methylene chloride (40 ml) at room temperature. The resultant 35 mixture was stirred at the same temperature for 3.5 hours.

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and the precipitated crystals were collected by filtration. The filtrate was washed with water, dried over magnesium sulfate, and concentrated to dryness in vacuo to give a crystalline residue, which was washed with isopropanol. The obtained crystals were combined and those dihydrochloride was obtained by treating with excess ethanolic hydrochloric acid. The dihydrochloride was recrystallized from a mixture of isopropanol and methanol to give 4-[(4-pyridyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine dihydrochloride (0.73 g).

mp : 190-194°C

IR (Nujol) : 1620, 1600, 1325, 1155, 1130  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.4-2.1 (4H, m), 2.6-4.2

(5H, m), 7.0-9.2 (13H, m), 11.67 (1H, s)

#### Example 6

(1) The following compound was prepared in a similar manner to that of Example 4 (2).

Phenyl 4-[(2-pyridyl)thio]-1-piperidine-carboxylate.

mp : 92-94°C

IR (Nujol) : 1720  $\text{cm}^{-1}$

NMR (DMSO- $\text{d}_6$ ,  $\delta$ ) : 1.35-2.5 (4H, m), 3.1-3.85

(3H, m), 3.85-4.5 (2H, m), 7.0-7.85 (8H, m),

8.35-8.65 (1H, m)

(2) The following compound was prepared in a similar manner to that of Example 4 (3).

4-[(2-Pyridyl)thio]piperidine dihydrochloride.

mp : 228-235°C

IR (Nujol) : 2800-2100  $\text{cm}^{-1}$

NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ) : 1.7-2.7 (4H, m), 3.25-4.5 (5H, m),  
7.7-8.85 (4H, m)

(3) m-Chloroperbenzoic acid (0.77 g) was added to

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an ice-cooled solution of 4-[(2-pyridyl)thio]piperidine dihydrochloride (1.0 g) in water (20 ml) and the mixture was stirred at the same temperature for 7.5 hours.

5 After additional m-chloroperbenzoic acid (0.07 g) and water (5 ml) were added, the mixture was stirred at the same temperature for 1 hour, adjusted to alkaline pH with sodium hydroxide solution, and extracted several times with chloroform. The extracts were combined, dried over magnesium sulfate, and concentrated in vacuo. The  
10 oily residue was dissolved in chloroform. The solution was treated with ethanolic hydrochloric acid and concentrated in vacuo. The crystalline residue was washed with isopropanol to give 4-[(2-pyridyl)sulfinyl]-piperidine hydrochloride (0.70 g).

15 mp : 213.5-215°C

IR (Nujol) : 2750-2400, 1040  $\text{cm}^{-1}$

NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ) : 1.35-2.8 (4H, m), 2.8-3.9 (5H, m),  
7.55-8.35 (3H, m), 8.65-9.0 (1H, m)

20 (4) 4-[[7-(Trifluoromethyl)-4-quinolyl]amino]-benzoyl chloride hydrochloride (0.69 g) was added slowly to a stirred mixture of 4-[(2-pyridyl)sulfinyl]-piperidine hydrochloride (0.50 g) and triethylamine (1.72 ml) in dry methylene chloride (22 ml) at room  
25 temperature. The resultant mixture was stirred at the same temperature for 1.5 hours and concentrated in vacuo. The residue was partitioned between chloroform and water. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and  
30 concentrated to dryness in vacuo. The resultant crystalline residue was recrystallized from a mixture of methylene chloride and methanol and washed successively with methanol and methylene chloride to give 4-[(2-pyridyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]-  
35 amino]benzoyl]piperidine (0.59 g).

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mp : 214-215.5°C

IR (Nujol) : 3325, 1610, 1565, 1040  $\text{cm}^{-1}$ NMR ( $\text{CDCl}_3$ - $\text{CD}_3\text{OD}$ ,  $\delta$ ) : 1.0-2.5 (4H, m), 2.5-3.65 (3H, m), 3.85-4.4 (2H, m), 7.0-8.8 (13H, m)

5

Example 7

4-[[7-(Trifluoromethyl)-4-quinolyl]amino]benzoyl chloride hydrochloride (1.0 g) was added slowly to a stirred mixture of 4-benzylpiperidine (0.45 g) and triethylamine (0.78 g) in dry methylene chloride (17 ml) at room temperature. The resultant mixture was stirred at the same temperature for 2 hours and diluted with an aqueous sodium bicarbonate. The precipitated powder was collected by filtration and the methylene chloride layer was concentrated to dryness in vacuo. The collected powder and the residue were combined, dissolved in ethyl acetate, washed with water, dried over magnesium sulfate, and concentrated to dryness in vacuo. The residue was treated with excess ethanolic hydrochloric acid to give the corresponding hydrochloride, which was triturated in ethyl acetate. The precipitated powder was collected and recrystallized from ethanol to give 4-benzyl-1-[4-[[7-(trifluoromethyl)-4-quinolyl]-amino]benzoyl]piperidine hydrochloride (0.51 g).

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mp : 240-242°C

IR (Nujol) : 3200-3020, 2550 (broad), 1635, 1620, 1590  $\text{cm}^{-1}$ NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 0.7-2.0 (5H, m), 2.75-3.2 (2H, m), 3.4-4.35 (4H, m), 6.93 (1H, d,  $J=7\text{Hz}$ ), 7.13 (5H, s), 7.48 (4H, s), 8.05 (1H, broad d,  $J=9\text{Hz}$ ), 8.63 (1H, broad s), 8.67 (1H, d,  $J=7\text{Hz}$ ), 9.15 (1H, broad d,  $J=9\text{Hz}$ ), 11.3 (1H, broad)

30

Example 8

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(1) 4-Nitrobenzoyl chloride (3.08 g) was added

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slowly to a stirred mixture of 4-(4-fluorobenzoyl)-  
piperidine hydrochloride (4.0 g) and triethylamine  
(4.98 g) in methylene chloride (110 ml) at room tempera-  
5 ture. The resulting mixture was stirred at this  
temperature for 1 hour, washed with 1N hydrochloric acid,  
saturated sodium bicarbonate solution, and brine, dried  
over magnesium sulfate and concentrated in vacuo.  
The residue was recrystallized from a mixture of acetone  
and methanol to give 4-(4-fluorobenzoyl)-1-(4-nitrobenzoyl)-  
10 piperidine (5.0 g) as colourless crystals.

mp : 168.5-170°C

IR (Nujol) : 1680, 1625, 1515, 1360, 1340  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.2-2.1 (4H, m), 2.85-4.15  
(4H, m), 4.15-4.8 (1H, m), 7.2-8.4 (8H, m)

15

(2) 4-(4-Fluorobenzoyl)-1-(4-nitrobenzoyl)-  
piperidine (4.75 g) was added slowly to a stirred mixture  
of iron powder (4.75 g), ammonium chloride (0.57 g),  
water (28.5 ml), ethanol (38 ml) and methyl cellosolve  
20 (76 ml) under reflux. The resulting mixture was stirred  
under reflux for 30 minutes and filtered. The filtrate  
was concentrated in vacuo. The residue was diluted  
with saturated sodium bicarbonate solution and  
extracted twice with methylene chloride. The extract  
25 was washed with brine, dried over magnesium sulfate and  
concentrated in vacuo. The resulting residue was  
recrystallized from ethanol to give 1-(4-aminobenzoyl)-4-  
(4-fluorobenzoyl)piperidine (3.6 g) as pale yellow  
crystals.

30

mp : 182-184°C

IR (Nujol) : 3460, 3440, 3320, 3210, 1675, 1635  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.3-2.1 (4H, m), 2.8-3.2 (2H,  
m), 3.4-3.95 (1H, m), 3.95-4.4 (2H, m), 5.43  
(2H, s), 6.55 (2H, d,  $J=8\text{Hz}$ ), 7.13 (2H, d,  
35  $J=8\text{Hz}$ ), 7.32 (2H, t,  $J=9\text{Hz}$ ), 8.07 (2H, m)

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(3) Sodium borohydride (0.058 g) was added to a solution of 1-(4-aminobenzoyl)-4-(4-fluorobenzoyl)-piperidine (1.0 g) in methanol (80 ml) and the mixture was stirred at room temperature for 2 hours. Additional sodium borohydride (0.050 g) was added. After being stirred at the same temperature for 1.5 hours, the resultant mixture was concentrated in vacuo. The residue was diluted with water and extracted twice with methylene chloride. The extracts were combined, washed with brine, dried over magnesium sulfate, and concentrated to dryness in vacuo. The powdery residue was washed with diisopropyl ether to give 1-(4-aminobenzoyl)-4-[(4-fluorophenyl)hydroxymethyl]piperidine (1.00 g) as pale yellow powder.

mp : 82°C (dec.)  
IR (Nujol) : 3350 (broad), 3240, 1605  $\text{cm}^{-1}$   
NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.1-4.5 (13H, m), 6.57 (2H, d,  $J=9\text{Hz}$ ), 6.8-7.4 (8H, m)

(4) A mixture of 4-chloro-7-(trifluoromethyl)-quinoline (0.32 g) and 1-(4-aminobenzoyl)-4-[(4-fluorophenyl)hydroxymethyl]piperidine (0.45 g) in dry ethanol (10 ml) was stirred under reflux for 4 hours and concentrated to dryness in vacuo. The residue was recrystallized from a mixture of ethyl acetate and isopropanol to give 4-[(4-fluorophenyl)hydroxymethyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]-piperidine hydrochloride (0.65 g) as pale yellow powder.

mp : 218-223°C  
IR (Nujol) : 3350, 3340, 2800-2400, 1620, 1600, 1580  $\text{cm}^{-1}$   
NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.0-4.5 (11H, m), 7.0-9.3 (13H, m), 11.5 (1H, broad)

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Example 9

(1) The following compound was prepared in a similar manner to that of Example 1 (3).

Phenyl 4-[(4-fluorophenyl)sulfonyl]-1-piperidine-carboxylate.

mp : 144-146°C (recrystallized from diisopropyl ether - ethyl acetate)

IR (Nujol) : 1710, 1320, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.45-2.2 (4H, m), 2.7-3.3 (3H, m), 4.3-4.55 (2H, m), 7.0-7.5 (7H, m), 7.8-8.05 (2H, m)

MS (m/e) : 363 ( $\text{M}^+$ ), 270 (base), 159, 143, 95, 77

(2) The following compound was prepared in a similar manner to that of Example 1 (4).

4-[(4-Fluorophenyl)sulfonyl]piperidine hydrochloride.

mp : 242-247°C (recrystallized from a mixture of ethanol and methanol)

IR (Nujol) : 2700, 2640, 2490, 1310, 1150  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.6-2.15 (4H, m), 2.7-3.9 (5H, m), 7.35-8.1 (4H, m), 9.35 (2H, broad)

MS (m/e) : 244 ( $\text{M}^+ + 1$ ), 243 ( $\text{M}^+$ ), 95, 84, 55 (base)

(3) The following compound was prepared in a similar manner to that of Example 1 (5).

4-[(4-fluorophenyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.

mp : 199-204°C (recrystallized from ethanol)

IR (Nujol) : 2650 (broad), 1635, 1610, 1585, 1320, 1140  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.2-2.2 (4H, m), 2.65-4.5 (5H, m), 7.0-9.35 (13H, m), 11.5 (1H, broad)

Example 10

(1) A mixture of ethyl 4-chloro-7-(trifluoromethyl)-

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3-quinoline-carboxylate (3.04 g) and 4-aminobenzoic acid (1.37 g) in tetrahydrofuran (53 ml) was stirred under reflux for 10 hours and cooled to room temperature. The precipitates were collected and washed with tetrahydrofuran to give 4-[[3-ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoic acid hydrochloride (2.69 g) as yellow powder.

mp : 256-257°C(dec.)

IR (Nujol) : 3300-3000, 1735, 1710, 1635  $\text{cm}^{-1}$

NMR ( $\text{CF}_3\text{COOH}$ ,  $\delta$ ) : 1.66 (3H, t,  $J=7\text{Hz}$ ), 4.68 (2H, quartet,  $J=7\text{Hz}$ ), 7.45-8.5 (7H, m), 9.4 (1H, m), 12.73 (1H, broad s)

(2) A suspension of 4-[[3-ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoic acid hydrochloride (2.51 g) in thionyl chloride (25 ml) was stirred under reflux for 4 hours and concentrated to dryness in vacuo to give 4-[[3-ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoyl chloride hydrochloride (2.62 g) as yellow powder.

mp : 202.5-223°C

IR (Nujol) : 2560 (broad), 1780, 1715, 1620  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.10 (3H, t,  $J=7\text{Hz}$ ), 3.78 (2H, quartet,  $J=7\text{Hz}$ ), 7.3-9.3 (8H, m), 11.8 (2H, broad s)

(3) 4-[[3-Ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoyl chloride hydrochloride (0.51 g) was added slowly to a stirred mixture of 4-(4-fluorophenyl)sulfonylpiperidine hydrochloride (0.31 g) and triethylamine (0.77 ml) in methylene chloride (8 ml) at room temperature. The resultant mixture was stirred at the same temperature for 2.5 hours and concentrated in vacuo. The residue was partitioned between chloroform and water. The organic layer was

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washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated to dryness in vacuo. The oily residue was treated with excess ethanolic hydrochloric acid to give hydrochloride, which was washed with ethanol to give 1-[4-[[3-ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]-4-[(4-fluorophenyl)sulfonyl]piperidine hydrochloride (0.67 g) as yellow powder.

mp : 231-233°C (dec.)

IR (Nujol) : 3120, 2580 (broad), 1730, 1645, 1625, 1300, 1140  $\text{cm}^{-1}$

NMR ( $\text{CF}_3\text{COOH}$ ,  $\delta$ ) : 1.57 (3H, t,  $J=7\text{Hz}$ ), 1.9-2.5 (4H, m), 3.0-5.25 (5H, m), 4.68 (2H, quartet,  $J=7\text{Hz}$ ), 7.3-8.3 (10H, m), 8.40 (1H, broad s), 9.45 (1H, broad s), 12.65 (1H, broad s)

#### Example 11

(1) An emulsion of phenyl 4-[2-fluorophenyl]thio]-1-piperidinecarboxylate (32 g) in a mixture of ethanol (317 ml) and 45% potassium hydroxide solution (197 ml) was stirred under reflux for 5 hours. The reaction mixture was evaporated in vacuo and the resultant aqueous mixture was extracted twice with chloroform. The extracts were combined and dried over magnesium sulfate. After removal of magnesium sulfate, the solution was treated with ethanolic hydrochloric acid and concentrated to dryness in vacuo. The residue was washed with ethyl acetate to give 4-[(2-fluorophenyl)thio]piperidine hydrochloride (19.1 g).

mp : 147-148.5°C (recrystallized from a mixture of ethyl acetate and isopropanol)

IR (Nujol) : 2800-2300  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.25-2.4 (4H, m), 2.85-3.85 (5H, m), 7.0-7.8 (4H, m), 9.35 (2H, broad s)

(2) 4-[[7-(Trifluoromethyl)-4-quinolyl]amino]-benzoyl chloride hydrochloride (26.6 g) was added slowly

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to a stirred mixture of 4-[(2-fluorophenyl)thio]piperidine hydrochloride (17.0 g) and triethylamine (47.7 ml) in dry methylene chloride (350 ml) at room temperature. The resultant mixture was stirred at the same temperature for 3 hours, and concentrated to dryness in vacuo. Water was added to the residue and the precipitated powder was collected by filtration, washed with water and diisopropyl ether, and dried to give a powder (35.5 g). The powder was recrystallized with following solvents to give 4-[(2-fluorophenyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]-amino]benzoyl]piperidine.

1) The object compound recrystallized from ethyl acetate

IR (Nujol) : 3200 (weak), 3160 (weak), 3070 (weak), 1645 (shoulder), 1630, 1580, 1570 (shoulder), 1530  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.0-2.25 (4H, m), 2.7-4.3 (5H, m), 7.0-8.8 (13H, m), 9.27 (1H, broad s)

X ray diffraction (Target, Cu; Filter, Ni; Voltage 30 KV; Current 10 m A; Time constant, 0.5 second; Scanning speed, 2°/minute; Chart speed 2 cm/minute; Divergence slit, 1°; Receiving slit, 0.15 m m; Scatter slit, 1°) :

peak No.	1	2	3	4	5
2 $\theta$ (Bragg diffraction angle)	7.7°	12.7°	13.4°	13.9°	15.8°
I/I <sub>0</sub> (relative intensity)	51	28	32	50	63

6	7	8	9	10	11	12	13
17.1°	19.6°	20.4°	21.7°	22.7°	23.6°	24.2°	25.2°
87	100	38	54	60	52	41	35

Thermal analysis [Atmosphere,  $\text{N}_2$  (30 ml/minute); Sensitivity, DSC  $\pm$  20 m J/S; Heating rate, 10°C/minute] :

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Phase transition (133°C) → melt (170°C) →  
phase transition → melt (201°C)

- 2) The object compound recrystallized from ethanol  
NMR values are the same as those of the above 1).

IR (Nujol) : 3350, 3050 (weak), 1610, 1570, 1530 cm<sup>-1</sup>

X ray diffraction [Analysis condition is the same  
as that of the above 1)] :

peak No.	1	2	3	4	5
2θ (Bragg diffraction angle)	7.6°	9.4°	11.1°	13.7°	15.4°
I/I <sub>0</sub> (relative intensity)	9	12	41	23	14

6	7	8	9	10	11	12	13	14	15
16.6°	17.0°	17.7°	18.7°	18.9°	19.2°	19.9°	20.4°	21.1°	21.7°
23	20	22	29	61	100	15	18	58	34

16	17	18	19	20	21	22	23
22.4°	23.5°	24.8°	26.5°	27.1°	27.5°	28.5°	29.3°
74	15	18	18	20	15	24	13

Thermal analysis [Analysis condition is the same  
as that of the above 1)] :

Melt (202°C)

- 3) The object compound recrystallized from acetone  
NMR values are the same as those of the above 1).

IR (Nujol) : 3160 (weak), 3060 (weak), 1640, 1580,  
1535 cm<sup>-1</sup>

X ray diffraction [Analysis condition is the same  
as that of the above 1)] :

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peak No.	1	2	3	4	5
2θ (Bragg diffraction angle)	8.0°	12.7°	13.5°	13.9°	14.4°
I/I <sub>0</sub> (relative intensity)	95	16	20	20	14

6	7	8	9	10	11	12	13	14	15
15.6°	17.1°	17.5°	18.5°	19.7°	10.1°	10.8°	11.3°	11.8°	13.3°
68	44	30	31	100	51	28	38	26	51

16	17	18	19	20	21	22
14.3°	15.2°	15.6°	16.4°	18.0°	18.3°	19.5°
18	23	21	20	24	18	21

Thermal analysis [Analysis condition is the same as that of the above 1)] :

Melt (172°C) → phase transition → melt (202°C)

(3) 4-[(2-Fluorophenyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine (1.34 g) was suspended in methanol. Excess ethanolic hydrochloric acid was added to the suspension and the resulting solution was concentrated in vacuo to give an oil. The oil was triturated in acetone to give 4-[(2-fluorophenyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]-amino]benzoyl]piperidine hydrochloride (1.11 g) as a powder.

1) The hydrochloride recrystallized from a mixture of water and acetone (1:1)

a) Crystallization temperature; 30 - 40°C

IR (Nujol) : 3130 (weak), 3080 (weak), 3030 (weak), 2700, 1650 (shoulder), 1615 (shoulder), 1590, 1570, 1550 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub>, δ) : 1.0-2.2 (4H, m), 2.7-4.4 (5H, m), 6.95-9.3 (13H, m), 11.6 (1H, broad)

X ray diffraction (Target, Cu; Filter, Ni; Voltage, 30 KV; Current, 10 mA; Time constant, 0.5 second; Scanning

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speed, 2°/minute; Chart speed 2 cm/minute; Divergence slit, 1°; Receiving slit, 0.15 m m; Scatter slit, 1°) :

peak No.	1	2	3	4	5
2θ (Bragg diffraction angle)	7.7°	8.8°	11.5°	15.9°	16.3°
I/I <sub>0</sub> (relative intensity)	17	19	42	30	30

6	7	8	9	10	11	12	13	14	15
17.6°	18.1°	19.3°	19.9°	21.0°	21.8°	22.8°	23.6°	25.0°	25.8°
84	41	27	42	100	22	32	22	22	37

16	17	18	19	20
27.1°	28.1°	28.3°	28.7°	29.3°
30	20	19	22	19

Thermal analysis (Atmosphere, N<sub>2</sub> (30 ml/minute); Sensitivity, DSC ± 20 m J/S; Heating rate 10°C/minute):

Melt (258°C)

b) Crystallization temperature; 0 - 30°C

NMR values are the same as those of the above a).

IR(Nujol): 3430(weak), 3200(weak), 3030(weak), 2680, 1620, 1595, 1530 cm<sup>-1</sup>

X ray diffraction[Analysis condition is the same as that of the above a)]:

peak number	1	2	3	4	5	6
2θ(Bragg diffraction angle)	9.7°	10.8°	15.4°	16.8°	17.3°	18.7°
I/I <sub>0</sub> (relative intensity)	34	34	45	66	69	100

7	8	9	10	11	12	13	14
19.6°	20.2°	21.8°	22.8°	24.0°	25.4°	28.0°	29.4°
79	69	55	45	90	59	45	38

The thermal Analysis[Analysis condition is the same as that of the above a)]:

Phase transition(215 - 224°C) - melt(257°C)

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2) The hydrochloride recrystallized from ethanol

NMR values are the same as those of the above 1) - a).

IR (Nujol) : 3370 (weak), 3200 (weak), 3030 (weak),  
2510, 1640 (shoulder), 1625 (shoulder), 1605,  
1590, 1560, 1535  $\text{cm}^{-1}$

X ray diffraction [Analysis condition is the same as that of the above 1) - a).

peak No.	1	2	3	4	5				
2θ (Bragg diffraction angle)	6.7°	9.3°	11.4°	12.4°	17.1°				
I/I <sub>0</sub> (relative intensity)	46	42	30	51	47				
6	7	8	9	10	11	12	13	14	15
18.7°	19.2°	19.9°	20.2°	21.6°	22.0°	23.5°	25.1°	25.7°	26.8°
48	54	100	77	41	37	28	99	44	25
16	17	18							
27.7°	28.3°	29.4°							
38	37	23							

Thermal Analysis [Analysis condition is the same as that of the above 1) - a).

Desolvation of ethanol (142°C) → phase transition → melt (231°C) → phase transition → melt (257°C)

2) The hydrochloride recrystallized from ethanolic hydrochloric acid

NMR values are the same as those of the above 1) - a).

IR (Nujol): 3200 (weak), 3140 (weak), 3040 (weak), 2710,  
1625, 1595, 1565, 1540  $\text{cm}^{-1}$

X ray diffraction [Analysis condition is the same as that of the above 1) - a)]:

peak No.	1	2	3	4	5			
2θ (Bragg diffraction angle)	7.5°	8.4°	9.7°	11.5°	12.1°			
I/I <sub>0</sub> (relative intensity)	19	13	15	16	23			
6	7	8	9	10	11	12	13	14
12.7°	13.1°	15.3°	15.9°	16.4°	17.1°	17.6°	17.9°	18.1°
27	26	23	18	18	35	42	42	34

15	16	17	18	19	20	21	22	23
18.5°	19.4°	21.1°	21.4°	21.9°	22.6°	22.9°	24.1°	24.3°
40	94	47	79	100	39	24	23	26
24	25	26	27	28	29	30		
24.9°	25.4°	26.8°	27.2°	28.1°	28.7°	29.5°		
24	21	23	24	34	24	28		

Thermal Analysis[Analysis condition is the same as that of the above 1)-a)]:

Melt(267°C)

(continued to the next page)

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Example 12

(1) 3-Chloroperbenzoic acid (0.76 g) was slowly added to a stirred solution of 4-[(2-fluorophenyl)thio]-piperidine hydrochloride (0.95 g) in a mixture of chloroform (71 ml) and methanol (4 ml) under ice-cooling over a period of 5 minutes and the reaction mixture was stirred at the same temperature for 1 hour. After being treated with sodium bisulfate solution under ice-cooling, the resultant mixture was adjusted to alkaline pH with 20% sodium hydroxide solution. The chloroform layer was separated and the aqueous layer was extracted three times with chloroform. The chloroform layers were combined and dried over magnesium sulfate. After removal of magnesium sulfate, the solution was treated with ethereal hydrochloric acid and concentrated to dryness in vacuo. The residue was washed with isopropanol to give 4-[(2-fluorophenyl)-sulfinyl]piperidine hydrochloride (0.48 g).

mp : 209-210°C

IR (Nujol) : 2850-2400, 1045  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.15-2.35 (4H, m), 2.75-3.7 (5H, m), 7.0-8.0 (4H, m), 8.85-9.65 (2H, broad s)

(2) The following compound was prepared in a similar manner to that of Example 3 (2).

4-[(2-Fluorophenyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.

mp : 221-222°C

IR (Nujol) : 3325, 1615, 1570, 1040  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3\text{-CD}_3\text{OD}$ ,  $\delta$ ) : 1.5-2.2 (4H, m), 2.8-3.23 (3H, m), 4.0-4.7 (2H, m), 7.1-8.67 (13H, m)

Example 13

(1) The following compound was prepared in a similar manner to that of Example 1 (3).

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Phenyl 4-[(2-thienyl)sulfonyl]-1-piperidine-carboxylate.

IR (Film) : 1715, 1700, 1310, 1140  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.15-2.25 (4H, m), 2.8-4.0

5 (3H, m), 4.1-4.65 (2H, m), 7.1-8.4 (8H, m)

(2) An emulsion of phenyl 4-[(2-thienyl)sulfonyl]-1-piperidine carboxylate (1.7 g) in a mixture of ethanol (39.8 ml) and 45% potassium hydroxide solution (24.5 ml) was stirred under reflux for 1.5 hours. Most of the ethanol was evaporated in vacuo and the resultant aqueous mixture was extracted three times with methylene chloride. The extracts were combined and dried over magnesium sulfate. After removal of magnesium sulfate, the solution was treated with ethanolic hydrochloric acid and concentrated to dryness in vacuo. The residue was washed with isopropanol to give 4-[(2-thienyl)sulfonyl]piperidine hydrochloride (1.17 g).

20 mp : 244-246°C

IR (Nujol) : 2800-2300, 1340, 1140  $\text{cm}^{-1}$

NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ) : 1.65-2.65 (4H, m), 2.65-3.35 (2H,

m), 3.35-4.0 (3H, m), 7.2-7.65 (1H, m),

7.75-8.25 (2H, m)

25

(3) The following compound was prepared in a similar manner to that of Example 4 (4).

4-[(2-Thienyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.

30 mp : 206-210°C (recrystallized from ethanol)

IR (Nujol) : 2700-2300, 1640, 1600, 1330, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ - $\text{CD}_3\text{OF}$ ,  $\delta$ ) : 1.5-2.4 (4H, m), 2.75-3.65

(3H, m), 3.85-4.4 (2H, m), 7.0-9.15 (13H, m)

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Example 14

(1) The following compound was prepared in a similar manner to that of Example 1 (1).

1-Methyl-4-[(2-thienyl)thio]piperidine.

IR (film) : 3070, 3000-2700  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.4-2.0 (6H, m), 2.2 (3H, s),  
2.3-3.15 (3H, m), 6.85-7.5 (3H, m)

(2) The following compound was prepared in a similar manner to that of Example 1 (2).

Phenyl 4-[(2-thienyl)thio]-1-piperidine-carboxylate.

IR (film) : 1740-1720  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.35-2.5 (4H, m), 2.85-3.5  
(3H, m), 4.0-4.5 (2H, m), 7.0-7.65 (8H, m)

(3) The following compound was prepared in a similar manner to that of Example 13 (2).

4-[(2-Thienyl)thio]piperidine hydrochloride.

mp : 175-177°C

IR (Nujol) : 2800-2300  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.4-2.35 (4H, m), 2.65-3.55  
(5H, m), 7.0-7.4 (2H, m), 7.65-7.85 (1H, m),  
9.15 (2H, broad s)

(4) The following compound was prepared in a similar manner to that of Example 3 (2).

4-[(2-Thienyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.

mp : 218.5-221°C

IR (Nujol) : 3300, 1620, 1610, 1580  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.0-2.35 (4H, m), 2.85-3.1 (3H, m),  
3.75-4.35 (2H, m), 7.0-8.85 (12H, m),  
9.33 (1H, s)

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Example 15

(1) The following compound was prepared in a similar manner to that of Example 3 (1).

4-[(2-Thienyl)sulfinyl]piperidine hydrochloride.

mp : 203-205°C

IR (Nujol) : 2800-2350, 1040  $\text{cm}^{-1}$

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.35-2.25 (4H, m),

2.65-3.35 (5H, m), 7.25 (1H, m),

7.55 (1H, m), 7.99 (1H, m), 9.27 (2H,

broad s)

(2) The following compound was prepared in a similar manner to that of Example 3 (2).

4-[(2-Thienyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.

mp : 220-221.5°C (recrystallized from methanol)

IR (Nujol) : 3230, 3160, 1620, 1580, 1020  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ - $\text{CD}_3\text{OD}$ ,  $\delta$ ) : 1.4-2.35 (4H, m),

2.9-3.5 (3H, m), 4.0-4.5 (2H, m),

7.1-8.65 (12H, m)

Example 16

(1) m-Chloroperbenzoic acid (1.20 g) was added to a stirred solution of 4-[(4-pyridyl)thio]piperidine dihydrochloride (1.33 g) in water (30 ml) under ice-cooling, and the mixture was stirred at the same temperature for 3 hours and then at room temperature for 5.5 hours. The resultant mixture was diluted with water and the pH of the mixture was adjusted to about 11 with 5% sodium hydroxide solution. The solution was extracted several times with chloroform. The extracts were combined, dried over magnesium sulfate, and concentrated in vacuo. The oily residue was crystallized from n-hexane and the crystals were recrystallized from a mixture of n-hexane and isopropanol to give 4-[(4-

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pyridyl)sulfinyl]piperidine (0.95 g).

mp : 73-76°C

IR (Nujol) : 3300, 3200, 1045  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.5-3.4 (10H, m), 7.4-9.0 (4H, m)

(2) The following compound was prepared in a similar manner to that of Example 6 (4).

4-[(4-Pyridyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.

mp : 196-198°C (recrystallized from a mixture of isopropanol and ethanol)

IR (Nujol) : 3330, 1615, 1570, 1040  $\text{cm}^{-1}$

NMR ( $\text{DMSO}-d_6$ ,  $\delta$ ) : 1.5-2.2 (4H, m), 3.0-4.5 (5H, m), 7.1-9.3 (14H, m)

#### Example 17

The following compound was prepared in a similar manner to that of Example 4 (4).

4-[(2-Pyridyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine dihydrochloride.

mp : 248-251°C

IR (Nujol) : 2650 (broad), 1620, 1610, 1600  $\text{cm}^{-1}$

NMR ( $\text{D}_2\text{O}$ ,  $\delta$ ) : 1.15-2.65 (4H, m), 3.0-4.65 (5H, m), 7.0-8.75 (13H, m)

#### Example 18

(1) A mixture of 4-[(2-pyridyl)thio]piperidine dihydrochloride (1.0 g) and 30% hydrogen peroxide (10 ml) in acetic acid (15 ml) was stirred at room temperature for 20 minutes and at 70°C for 2.5 hours. The mixture was treated with excess sodium sulfite solution and concentrated in vacuo. The residue was diluted with water, adjusted to alkaline pH with 5N aqueous potassium hydroxide solution, and extracted three times with chloroform. The extracts were combined, dried over

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magnesium sulfate, and concentrated in vacuo. The oily residue was dissolved in chloroform and treated with ethanolic hydrochloric acid. The solution was concentrated to dryness in vacuo. The solid residue was washed with isopropanol to give 4-[(2-pyridyl)sulfonyl]piperidine hydrochloride (0.84 g).

mp : 246.5-248°C

IR (Nujol) : 2800-2500, 2450, 1330, 1140  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ - $\text{CD}_3\text{OD}$ ,  $\delta$ ) : 2.0-2.65 (4H, m),

2.85-4.0 (5H, m), 7.45-7.85 (1H, m),

8.0-8.35 (2H, m), 8.65-8.95 (1H, m)

(2) The following compound was prepared in a similar manner to that of Example 4 (4).

4-[(2-Pyridyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.

mp : 193°C (dec.)

IR (Nujol) : 2750-2300, 1620, 1600, 1330, 1140  $\text{cm}^{-1}$

NMR ( $\text{CF}_3\text{COOH}$ ,  $\delta$ ) : 1.7-2.85 (4H, m), 3.0-5.35

(5H, m), 7.0-9.85 (13H, m)

#### Example 19

(1) 1-Benzyl-4-(4-fluorophenoxy)piperidine hydrochloride (3.85 g) was converted to the corresponding free base by treatment with sodium hydroxide solution and extraction with methylene chloride. Phenyl chloro-carbonate (2.8 g) was added dropwise to a stirred solution of the free base in dry methylene chloride (38.5 ml) under ice-cooling. The mixture was stirred at room temperature for 2 hours, washed successively with 1N sodium hydroxide solution, 1N hydrochloric acid, and brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was washed with diethyl ether to give phenyl 4-(4-fluorophenoxy)-1-piperidine carboxylate (2.18 g).

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mp : 98.5-100.5°C

IR (Nujol) : 1730, 1700  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.35-1.4 (4H, m), 3.1-4.15  
(4H, m), 4.35-4.85 (1H, m), 6.9-7.65 (9H, m)

5

(2) The following compound was prepared in a similar manner to that of Example 13 (2).

4-(4-Fluorophenoxy)piperidine hydrochloride.

mp : 155-156°C (recrystallized from a mixture of diisopropyl ether and isopropanol)

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IR (Nujol) : 2800-2300, 1220  $\text{cm}^{-1}$

(3) The following compound was prepared in a similar manner to that of Example 4 (4).

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4-(4-Fluorophenoxy)-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.

mp : 260-263°C (recrystallized from ethanol).

IR (Nujol) : 2700, 1620, 1590  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 1.35-2.3 (4H, m), 3.0-4.3

20

(4H, m), 4.5-5.0 (1H, m), 7.05-9.4 (13H, m)

#### Example 20

The following compound was prepared in a similar manner to that of Example 4 (4).

25

4-[(4-Fluorophenyl)amino]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine dihydrochloride.

mp : 212.5-215°C (recrystallized from a mixture of ethyl acetate and ethanol)

IR (Nujol) : 2850-2300, 1620, 1600  $\text{cm}^{-1}$

30

NMR ( $\text{CDCl}_3$ - $\text{CD}_3\text{OD}$ ,  $\delta$ ) : 1.65-2.5 (4H, m), 2.65-4.4  
(5H, m), 7.0-9.2 (13H, m)

#### Example 21

The following compound was prepared in a similar manner to that of Example 6 (4).

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1-[4-[[3-Ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]-4-[(4-fluorophenyl)thio]-piperidine.

mp : 129.5-132.5°C (recrystallized from a mixture of n-hexane and ethyl acetate)

IR (Nujol) : 3240, 3180, 1680, 1630  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.47 (3H, t, J=7Hz), 1.15-2.2 (4H, m), 2.55-3.45 (3H, m), 3.85-4.5 (2H, m), 4.46 (2H, quartet, J=7Hz), 6.8-7.55 (9H, m), 7.77 (1H, d, J=8Hz), 8.29 (1H, s), 9.31 (1H, s), 10.47 (1H, s)

#### Example 22

The following compound was prepared in a similar manner to that of Example 6 (4).

1-[4-[[3-Ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]-4-[(4-fluorophenyl)sulfinyl]-piperidine.

mp : 162-165°C (recrystallized from a mixture of diisopropyl ether and ethyl acetate)

IR (Nujol) : 3230, 3170, 1680, 1620, 1595, 1035  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.47 (3H, t, J=7Hz), 1.6-2.0 (4H, m), 2.45-3.1 (3H, m), 4.15-4.5 (2H, m), 4.44 (2H, quartet, J=7Hz), 6.95-7.85 (10H, m), 8.33 (1H, s), 9.37 (1H, s), 10.5 (1H, s)

#### Example 23

The following compounds were prepared in a similar manner to that of Example 8 (4).

(1) 4-[(2-Fluorophenyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.

IR (Nujol) : 3220-3040 (m), 2500 (broad), 1610, 1590, 1320, 1150  $\text{cm}^{-1}$

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- (2) 4-[(4-Fluorophenyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.  
IR (Nujol) : 3300, 1610  $\text{cm}^{-1}$
- 5 (3) 4-[(4-Fluorophenyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.  
IR (Nujol) : 3320, 1615, 1565, 1040  $\text{cm}^{-1}$
- 10 (4) 4-[(4-Pyridyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine dihydrochloride.  
IR (Nujol) : 2560, 1620, 1590  $\text{cm}^{-1}$
- 15 (5) 4-[(4-Pyridyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine dihydrochloride.  
IR (Nujol) : 1620, 1600, 1325, 1155, 1130  $\text{cm}^{-1}$
- 20 (6) 4-[(2-Pyridyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.  
IR (Nujol) : 3325, 1610, 1565, 1040  $\text{cm}^{-1}$
- (7) 4-Benzyl-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.  
IR (Nujol) : 3200-3020, 2550 (broad), 1635, 1620, 1590  $\text{cm}^{-1}$
- 25 (8) 4-[(4-Fluorophenyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.  
IR (Nujol) : 2650 (broad), 1635, 1610, 1585, 1320, 1140  $\text{cm}^{-1}$
- 30 (9) 1-[4-[[3-Ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]-4-[(4-fluorophenyl)sulfonyl]piperidine hydrochloride.  
IR (Nujol) : 3120, 2580 (broad), 1730, 1645, 1625, 1300, 1140  $\text{cm}^{-1}$
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- (10) 4-[(2-Fluorophenyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.  
IR (Nujol) : 3670-3150, 1640, 1580  $\text{cm}^{-1}$
- 5 (11) 4-[(2-Fluorophenyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.  
IR (Nujol) : 3325, 1615, 1570, 1040  $\text{cm}^{-1}$
- 10 (12) 4-[(2-Thienyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.  
IR (Nujol) : 2700-2300, 1640, 1600, 1330, 1140  $\text{cm}^{-1}$
- 15 (13) 4-[(2-Thienyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.  
IR (Nujol) : 3300, 1620, 1610, 1580  $\text{cm}^{-1}$
- 20 (14) 4-[(2-Thienyl)sulfinyl]-1-[4-[[7-trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.  
IR (Nujol) : 3230, 3160, 1620, 1580, 1020  $\text{cm}^{-1}$
- 25 (15) 4-[(4-Pyridyl)sulfinyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine.  
IR (Nujol) : 3330, 1615, 1570, 1040  $\text{cm}^{-1}$
- 30 (16) 4-[(2-Pyridyl)thio]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine dihydrochloride.  
IR (Nujol) : 2650 (broad), 1620, 1610, 1600  $\text{cm}^{-1}$
- 35 (17) 4-[(2-Pyridyl)sulfonyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.  
IR (Nujol) : 2750-2300, 1620, 1600, 1330, 1140  $\text{cm}^{-1}$
- (18) 4-(4-Fluorophenoxy)-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.

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IR (Nujol) : 2700, 1620, 1590  $\text{cm}^{-1}$

(19) 4-[(4-Fluorophenyl)amino]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine dihydrochloride.

5 IR (Nujol) : 2850-2300, 1620, 1600  $\text{cm}^{-1}$

(20) 1-[4-[[3-Ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]-4-[(4-fluorophenyl)thio]piperidine.

10 IR (Nujol) : 3240, 3180, 1680, 1630  $\text{cm}^{-1}$

(21) 1-[4-[[3-Ethoxycarbonyl-7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]-4-[(4-fluorophenyl)sulfinyl]piperidine.

15 IR (Nujol) : 3230, 3170, 1680, 1620, 1595,  
1035  $\text{cm}^{-1}$

Example 24

The following compound was prepared in a similar manner to that of Example 1 (5).

20

4-[(4-fluorophenyl)hydroxymethyl]-1-[4-[[7-(trifluoromethyl)-4-quinolyl]amino]benzoyl]piperidine hydrochloride.

25

IR(Nujol) : 3350, 3340, 2800-2400, 1620, 1600, 1580  $\text{cm}^{-1}$

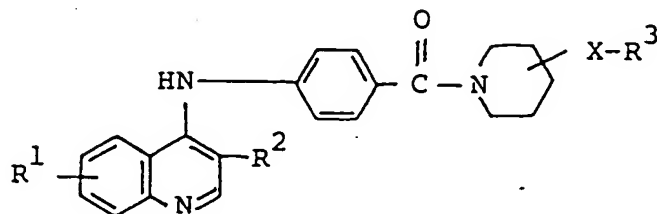
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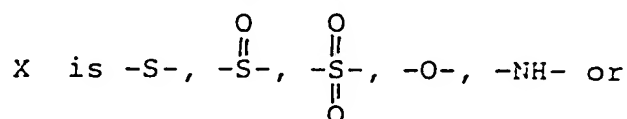
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We claim :

1. A piperidine compound of the formula :

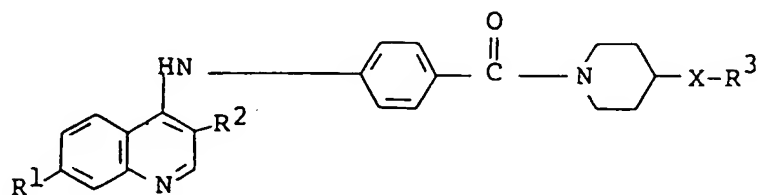


wherein  $R^1$  is hydrogen or trihalomethyl,  
 $R^2$  is hydrogen or protected carboxy,  
 $R^3$  is heterocyclic group or aryl which may  
have halogen and



lower alkylene which may have hydroxy,  
or pharmaceutically acceptable salt thereof.

2. A piperidine compound according to claim 1 which is represented by the formula:



wherein  $R^2$ ,  $R^3$  and X are each as defined above, and  
 $R^1$  is trihalomethyl,  
or pharmaceutically acceptable salt thereof.

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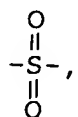
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3. A piperidine compound according to claim 2,  
in which  $R^1$  and X are each as defined in claim 2,  
 $R^2$  is hydrogen or esterified carboxy and  
 $R^3$  is 5 or 6-membered heteromonocyclic group  
containing nitrogen or sulfur atom or  
phenyl which may have halogen.

4. A piperidine compound according to claim 3,  
in which  $R^1$  and X are each as defined in claim 3,  
 $R^2$  is hydrogen or lower alkoxy carbonyl and  
 $R^3$  is pyridyl, thienyl or phenyl  
which may have halogen.

5. A piperidine compound according to claim 4,  
in which  $R^1$  is trifluoromethyl,  
 $R^2$  is hydrogen or  
ethoxycarbonyl,  
 $R^3$  is pyridyl,  
thienyl or  
fluorophenyl and

X is -S-,



-O-,

-NH-,

-CH<sub>2</sub>- or



6. A piperidine compound according to claim 5,  
in which  $R^1$  is trifluoromethyl,  
 $R^2$  is hydrogen,

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$R^3$  is fluorphenyl and

X is -S- or  $\begin{array}{c} \text{O} \\ \parallel \\ \text{-S-} \\ \parallel \\ \text{O} \end{array}$ .

5

7. A piperidine compound according to claim 6,  
which is 4-[(2-fluorophenyl)thio]-1-[4-  
[[7-(trifluoromethyl)-4-quinolyl]amino]-  
benzoyl]piperidine or pharmaceutically acceptable  
salt thereof.

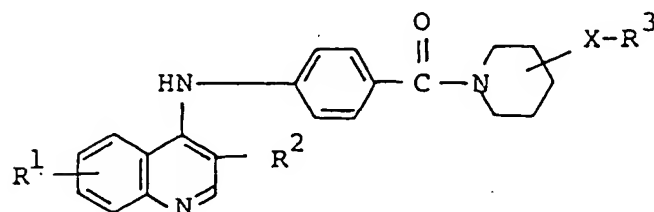
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8. A piperidine compound according to claim 6,  
which is 4-[(2-fluorophenyl)sulfonyl]-1-[4-  
[[7-(trifluoromethyl)-4-quinolyl]amino]-  
benzoyl]piperidine or pharmaceutically acceptable  
salt thereof.

15

9. A process for preparing a piperidine compound of  
the formula :

20



25

wherein  $R^1$  is hydrogen or trihalomethyl,  
 $R^2$  is hydrogen or protected carboxy,  
 $R^3$  is heterocyclic group or aryl which  
may have halogen and

30

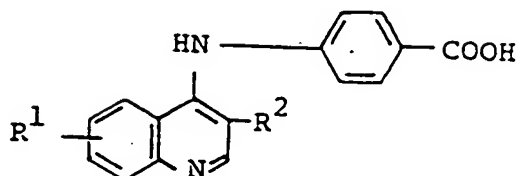
X is -S-,  $\begin{array}{c} \text{O} \\ \parallel \\ \text{-S-} \\ \parallel \\ \text{O} \end{array}$ ,  $\begin{array}{c} \text{O} \\ \parallel \\ \text{-S-} \\ \parallel \\ \text{O} \end{array}$ , -O-, -NH- or lower

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alkylene which may have hydroxy,  
or salt thereof,  
which comprises,

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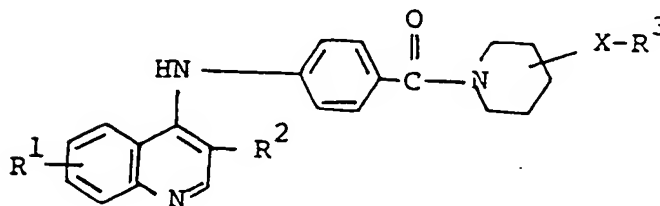
(a) reacting a compound of the formula :



10 wherein R<sup>1</sup> and R<sup>2</sup> are each as defined above,  
or its reactive derivative  
at the carboxy group  
or salt thereof,  
15 with a compound of the formula :



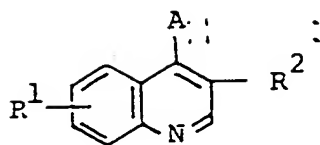
20 wherein R<sup>3</sup> and X are each as defined above,  
or its reactive derivative at the amino group  
or salt thereof,  
to give a compound of the formula :



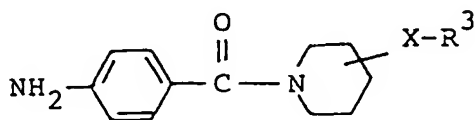
30 wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each as defined above,  
or salt thereof or;

35 (b) reacting a compound of the formula :

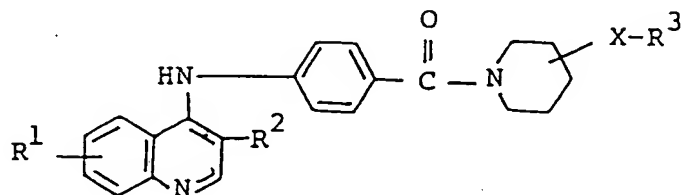
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wherein  $R^1$  and  $R^2$  are each as defined above,  
or salt thereof,  
with a compound of the formula :



wherein  $R^3$  and X are each as defined above,  
or salt thereof,  
to give a compound of the formula :



wherein  $R^1$ ,  $R^2$ ,  $R^3$  and X are each as defined above,  
or salt thereof.

10. A pharmaceutical composition comprising, as an effective ingredient, one or more piperidine compound of claim 1 or salt thereof and pharmaceutically acceptable carrier(s).
11. The piperidine compound of claim 1 for use as an antihypertensive agent.



(12)

**EUROPEAN PATENT APPLICATION**

(21) Application number: 86300808.2

(22) Date of filing: 06.02.86

(51) Int. Cl.<sup>3</sup>: **C 07 D 401/12**  
**C 07 D 401/14, C 07 D 409/1-**  
**4**  
**A 61 K 31/47**

(30) Priority: 11.02.85 GB 8503416  
 12.07.85 GB 8517675

(43) Date of publication of application:  
 20.08.86 Bulletin 86/34

(88) Date of deferred publication of search report: 02.09.87

(84) Designated Contracting States:  
 AT BE CH DE FR GB IT LI LU NL SE

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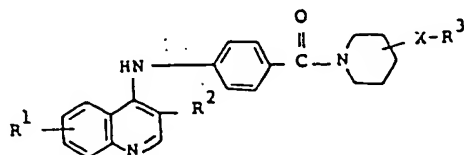
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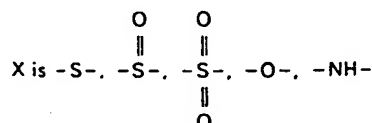
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(54) Piperidine compound.

(57) This invention provides a piperidine compound of the formula:



wherein R<sup>1</sup> is hydrogen or trihalomethyl,  
 R<sup>2</sup> is hydrogen or protected carboxyl  
 R<sup>3</sup> is heterocyclic group or aryl which may have halogen,  
 and



or lower alkylene which may have hydroxy, and pharmaceu-  
 tically acceptable salt thereof. This compound possesses  
 hypotensive activity and are useful as anti-hypertensive

agent. The invention further relates to processes for the  
 preparation of this compound and pharmaceutical composi-  
 tion comprising compound of the above formula.



EP 86 30 0808

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
Y	US-A-3 875 165 (J.L. ARCHIBALD)  * Claim 1; column 4, lines 14-65; column 6, line 56; column 7, lines 21-24 *	1,9,10 ,11	C 07 D 401/12 C 07 D 401/14 C 07 D 409/14 A 61 K 31/47
Y	--- EP-A-0 001 175 (WYETH) * Claims 1,13,15 *	1,9,10	
A	--- US-A-4 167 567 (J.M. McCALL)  * Claims 1,18,29; column 1, scheme A *	1,9,10 ,11	
A	--- US-A-4 166 853 (J.M. McCALL)  * Claims 1,15; column 1, scheme A; column 2, lines 61-65 *	1,9,10 ,11	
P,Y	--- PATENT ABSTRACTS OF JAPAN, vol. 10, no. 94 (C-338)[2151], 11th April 1986; & JP-A-60 226 877 (FUJISAWA YAKUHI KOGYO K.K.) 12-11-1985 * Abstract *	1,9,10 ,11	C 07 D 401/00 C 07 D 409/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 27-05-1987	Examiner SCARPONI U.
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons  & : member of the same patent family, corresponding document	